CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY DEPARTMENT OF PESTICIDE REGULATION MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

BORIC ACID AND RELATED INORGANIC BORATES

Chemical Code # 000769, Tolerance # 50366 SB 950 # 236

August 26, 1987 Revised 7/10/89, 1/15/92, 7/24/92, 8/7/92, and 1/20/95

I. DATA GAP STATUS

Chronic toxicity, rat: Data gap, inadequate studies on file, possible adverse effect

indicated

Chronic toxicity, dog: Data gap, inadequate studies on file, possible adverse effect

indicated

Oncogenicity, rat: Data gap, no study on file

Oncogenicity, mouse: No data gap, possible adverse effects (not neoplasia)

Reproduction, mouse: Data gap, inadequate studies on file, possible adverse effect

indicated

Teratology, rabbit: No data gap, possible adverse effect

DPR MEDICAL TOXICOLOGY BORIC ACID AND RELATED INORGANIC BORATES T950120

Page 2

Teratology, rat: No data gap, possible adverse effect

Teratology, mouse**o:** No data gap, possible adverse effect

Gene mutation: No data gap, no adverse effect

Chromosomal effects: No data gap, no adverse effect

DNA damage: No data gap, possible adverse effect

Neurotoxicity: Not required at this time

There are now acceptable teratology studies in 3 species, including rat. For the purpose of filling data gaps, the following active ingredients have been grouped together: Boric acid (SB # 236, tolerance # 50366, lead chemical), boric oxide (SB # 535, tolerance # 50683), borax (SB # 534, tolerance # 50198), sodium metaborate (SB # 870, tolerance # 50680), disodium octaborate tetrahydrate (SB # 657, tolerance # 50681), and sodium tetraborate (pentahydrate) (SB # 875, tolerance # 50682). Studies in the SB-950 database for these chemicals were conducted with boric acid and borax.

Note, Toxicology one-liners are attached: All record numbers for studies mandated under SB-950 for the above active ingredients were examined. The highest [current series] record number examined was # 131754 (Document No. 50366-098). A few record numbers > 900000 exist, and were also examined. Reconciliation was with library printouts dated Dec. 5, 1994.

Original toxicology summary by J. Carlisle. Revisions by J. Gee, 7/10/89; Kishiyama, Aldous, and Gee 1/15/92; Aldous, 7/24/92; Gee, 8/7/92; Aldous and Gee, 1/20/95.

Filename T950120

DPR MEDICAL TOXICOLOGY BORIC ACID AND RELATED INORGANIC BORATES T950120

Page 3

Note: these pages contain summaries only. Individual worksheets may identify additional effects.

Note: in the one-liners of the Summary below:

** indicates an acceptable study.

Bold face indicates a possible adverse effect.

II. TOXICOLOGY SUMMARY

COMBINED, RAT

50366-078 088705 Draft protocol for combined rat study, dated 7/17/90. CDFA review of 8/14/90 noted that the protocol appeared to be appropriate. A few comments were made by CDFA reviewer, J. Gee.

CHRONIC, RAT (See also supplementary data at the end of the Summary of Toxicology Data for relevant subchronic studies)

50366-048 959678, "Two-year Dietary Administration - Albino Rats, Boric Acid, Final Report". (Hazleton Laboratories, Inc., Falls Church, VA, # 182-104, 7/8/66). Boric acid, 98.69% - 100.02%, was fed in the diet for 2 years at 0, 670, 2000, or 6700 ppm (equivalent to 117, 350 and 1170 ppm elemental boron); 35 rats/sex/level with 70/sex for controls. Interim sacrifices of 5/sex/dose at 6 and 12 months. No ophthalmology. Nominal NOEL = 2000 ppm (0.20%), based on the following adverse effects: decreased b.w. (-19% in males and -28% in females at termination), reduced hemoglobin, atrophic testes in all high dose males at 6, 12 and 24 month sacrifices, lower liver weight and lack of ovulation, discharge from eyes with eyelid gland changes. UNACCEPTABLE, not upgradeable (too few animals for an oncogenicity study, inadequate

histopathology with only 10/sex/dose at term although more survived, limited sampling for diet analysis and results not reported, no eyes for histopathology and no ophthalmology). (Gee, 6/27/85 and 6/26/89).

NOTE: The memo from EPA to CDFA addressing differences in data gap status for this chemical (dated 2/7/89) notes EPA classification as "minimum".

50366-048 035663 Addendum to 048 959678 - Boron content of tissues.

50198-010 038963 "Two-year Dietary Administration - Albino Rats." (Hazleton, VA, 7/8/66, project no. 182-104). Borax (sodium tetraborate decahydrate), at approximately 104% theoretical boron content, fed in the diet at 0, 0.103, 0.308 or 1.03% (equivalent to 117, 350 and 1170 ppm of elemental boron) of the diet to 70/sex control group and 35/sex/dose for 2 years; 5/sex/group were sacrificed at 6 and 12 months. NOEL = 0.103% (decreased body weight gain); NOAEL = 0.308% (testicular atrophy); possible adverse effect (testicular atrophy); unacceptable (inadequate tissues, clinical chemistry parameters, no ophthalmological exam, not all surviving animals subjected to histopathology, no results of analyses of diet samples taken during study) - not upgradeable. Gee, 6/22/89.

50681-006 068030 duplicate of 50198-010 038963.

50366-051 035659, "The Toxicity of Boric Acid and Sodium Tetraborate: A Literature Review", (U.S. Borax Research Corp., Griffin, T.S., 8/29/78). References include Weir, R.J. Jr., and Fisher, R.S., 1972, Toxicologic Studies on Borax and Boric Acid;

Toxicol. and Appl. Pharmacol. 23: 351" which summarizes information in 048 959678.

UNACCEPTABLE (summary information only). (Carlisle 8/11/87)

NOTE: The memo from EPA to CDFA addressing differences in data gap status for this chemical (dated 2/7/89) notes EPA classification as "supplementary".

See also the summary for Borax, SB#534.

CHRONIC, DOG

50366-078 088706 Draft protocol for chronic dog study, dated 7/17/90. CDFA review of 8/14/90 noted that protocol appeared to be appropriate. A few comments were made by CDFA reviewer, J. Gee.

50366-047 959663, "38-Week Dietary Feeding - Dogs, Boric Acid, Final Report", (Hazleton Laboratories, Inc., Falls Church, VA., 2/28/67), boric acid $\geq 99.94\%$ purity, fed in the diet for 38 weeks at 0 or 6700 ppm (equivalent to 1170 ppm elemental boron); 4 beagle dogs/sex with 2/sex necropsied at 26 weeks. Hematology, clinical chemistry and urinalysis at several intervals with basic parameters measured. No ophthalmology and no eye tissues for histological examination. No evidence of boron accumulation in selected tissues. NOEL < 6700 ppm, based on testicular atrophy (seen at 26 weeks and 38 weeks) and inactive ovaries. UNACCEPTABLE, not upgradeable (only 38 weeks, only 1 dose level). (Remsen (Gee) 6/26/85 and 6/26/89)

NOTE: The memo from EPA to CDFA addressing differences in data gap status for this chemical (dated 2/7/89) notes EPA classification as "supplementary".

50681-005 067520 Weir, R.J., "38-week dietary feeding - dogs: Borax (sodium tetraborate decahydrate)", Hazleton Laboratories, Inc., 2/28/67. Four beagles per sex were given control or 1.03% borax in diet. Two/sex/group were sacrificed at wk 26. The other two controls/sex and one treated dog/sex were sacrificed at wk 38. The remaining dog/sex on treatment was placed on control diet for 25 days prior to sacrifice. "Testicular atrophy and spermatogenic arrest" were attributed to treatment, a "possible adverse effect". Investigators described the male recovery study dog as having a "moderate degree of degeneration and evidence of complete cessation of spermatogenesis". Varying degrees of testicular degeneration or atrophy in controls confounded interpretation, however investigators considered that testicular atrophy was a probable treatment effect. Study is not acceptable, and not upgradeable (no NOEL identified, only one dose level, too few animals under any given dosing regimen, too few tissues examined, no ophthalmology), but provides useful information. Aldous, 12/04/91.

"Two-Year Dietary Feeding - Dogs Borax (sodium tetraborate decahydrate) Final Report." (Hazleton Laboratories, VA, 7/8/66, project no. 182-106) Borax, average of 104% theoretical boron content, fed to beagle dogs at 0, 0.051, 0.103 or 0.309% (equivalent to 59, 117 and 350 ppm as elemental boron) of the diet for 1 or 2 years; 4/sex/dose; 1/sex/dose sacrificed after 1 year, 2 - 3/sex/dose after 2 years with 1/sex in control and high dose fed control diet for 3 months after 2 years for a recovery study; boron levels in blood, urine, feces and selected tissues measured at several intervals; possible adverse effects on sperm motility and count at 0.309%; NOEL/NOAEL cannot be determined since sperm viability was not measured at 0.51 and 0.103%; unacceptable (inadequate tissues for histology, no ophthalmology, no analysis of diet, no NOEL determined) Gee, 6/23/89.

50681-007 068031 Duplicate of 50198-011 038964.

DPR MEDICAL TOXICOLOGY

50681-005 067519 Paynter, O. E. "90-Day dietary feeding - Dogs: with 20 MULE TEAM* Borax (Sodium tetraborate decahydrate)". Hazleton Laboratories, Inc., 1/17/63. Five beagles per sex were dosed with 0, 0.0154, 0.154, or 1.54% borax in diet. Testicular atrophy was noted at 1.54% as the principal finding (no changes in testes were attributed to treatment at lower dosages). Small changes in morphology of adrenal cortex and in thyroids of females were noted at 0.154%. The testicular effects are "possible adverse effects", however this study is not pivotal, since lower NOELs for testicular atrophy and/or changes in sperm quality have been noted in dog studies of longer duration, as noted in one-liners above. Aldous, 1/14/92 (no worksheet).

50366-049 959677 "Two-Year Dietary Feeding -Dogs, Boric Acid, Final Report", (Hazleton Laboratories, Inc., Falls Church, VA., # 182-106, 7/8/66), Boric Acid ≥ 98.6% purity, fed in the diet for 2 years at 0, 330, 670, or 2000 ppm (equivalent to 58, 117 and 350 ppm as elemental boron); 4 beagle dogs/sex/level (1/sex/level sacrificed at 1 yr). NOEL = 670 ppm based on the following adverse effects seen at 2000 ppm: slight microscopic changes in testes and increased epithelial nests in thyroid. UNACCEPTABLE, not upgradeable(no toxicity at high dose, no ophthalmology, no analysis of diet for content of boron, limited list of tissues for histopathology). (Remsen (Gee) 6/27/85 and 6/26/89)

NOTE: The memo from EPA to CDFA addressing differences in data gap status for this chemical (dated 2/7/89) notes EPA classification as "minimum".

50366-049 035664, Addendum to 049 959677

50366-051 035659, "The Toxicity of Boric Acid and Sodium Tetraborate: A Literature Review", (U.S. Borax Research Corp., Griffin, T.S., 8/29/78). References include Weir, R.J. Jr., and Fisher, R.S., 1972, Toxicologic Studies on Borax and Boric Acid; Toxicol. and Appl. Pharmacol. 23: 351 which summarizes information in 049 959677. UNACCEPTABLE (summary information only). (Carlisle 8/11/87)

NOTE: The memo from EPA to CDFA addressing differences in data gap status for this chemical (dated 2/7/89) notes EPA classification as "supplementary".

See also the summary for Borax, SB#534.

ONCOGENICITY, RAT

No study on file. See under CHRONIC RAT above.

ONCOGENICITY, MOUSE

** 50366-070 065131 "Toxicology and Carcinogenesis Studies of Boric Acid in B6C3F₁ Mice (Feed Studies)." (EG&G Mason Research Institute for NTP, October, 1987, Technical Report Series, No. 324) Boric acid,99.7%; fed to B6C3F₁ mice, 50/group, at 0 (diet), 2500 or 5000 ppm for 103 weeks; NOEL < 2500 ppm (decreased weight gain and survival), NOAEL = 2500 ppm (testicular atrophy and interstitial cell hyperplasia at 5000 ppm); ACCEPTABLE with a possible adverse effect. (Gee, 6/21/89).

50366-068 065464 Exact duplicate of 065131 (from another registrant).

DPR MEDICAL TOXICOLOGY BORIC ACID AND RELATED INORGANIC BORATES T950120
Page 8

50366-067 075634 Exact duplicate of 065131.

50366-071 067243 Exact duplicate of 065131 (deleted from system).

REPRODUCTION, RAT

Note: The most recent reproduction data are in the mouse (see separate section below).

50198-012 038965 "Three-Generation Reproduction Study - Rats; Borax (Sodium Tetraborate Decahydrate) - Final Report." (Hazleton Laboratories, VA, 7/8/66, project no. 182-105)
Borax, no purity stated; fed in the diet to rats at 0, 0.103, 0.308 or 1.03% (equivalent to 117, 350 and 1170 ppm elemental boron), 8 males and 16 females per group; three generations, 2 litters per generation for low and mid doses; complete infertility at 1.03% - possible adverse effect (testicular atrophy and lack of viable sperm, decreased ovulation, infertility at nominal 1.03%); NOAEL (nominal) = 0.308% based on reproductive effects and clinical signs in adults. Unacceptable but possibly upgradeable (no diet analysis, no histopathology on F1 and F2 adult breeders at low and mid dose although tissues were saved, no purity of borax, no individual data). Gee, 6/23/89.

50681-008 068032 Duplicate of 50198-012 038965.

50366-049 959681, "Three-Generation Reproduction Study - Rats, Boric Acid, Final Report", (Hazleton Laboratories, Inc., Falls Church, VA., # 182-105, 7/8/66) Boric acid ≥ 98.69% purity, fed in the diet for 3 generations, 3 litters/generation at 0, 670, 2000, and 6700 ppm, 8 males and 16 females per group. Apparent NOEL = 2000 ppm, based on the following adverse effects seen at 6700 ppm; general (decreased bodyweight, poor appearance) and reproductive (small, soft testes; congested or cystic ovaries; no conceptions). High dose females were mated with control males - 1 litter and 3 abortions; UNACCEPTABLE, (no histopathology on F1 parents although tissues were taken; no analysis of diet, husbandry problems, no individual

data). Possibly upgradeable with submission of missing data. (Remsen (Gee) 6/27/85 and 7/7/89)

50366-051 035660, "The Toxicity of Boric Acid and Sodium Tetraborate: A Literature Review", (U.S. Borax Research Corp., Griffin, T. S., 8/29/78) Includes 3 references to articles related to reproductive effects. The first article reports no effects on fertility in rats given single oral doses of 45, 150, or 450 mg/kg as boron, and no reproductive effects of changes in serum chemistry, body, testis, seminal vesicle or prostate weights in rats exposed to drinking water containing 0.3, 1, or 6 mg/l boron (1 mg boric acid = 0.175 mg boron). Another study reported gonadotropic effects at a drinking water concentration of 6 mg/l. A third study reported decreased b.w. gain, and smaller testes or ovaries after 7 weeks at 300 mg/l drinking water, with a NOEC of 75 to 150 mg/l. UNACCEPTABLE (summary information only). (Carlisle, 8-11-87).

See also the summary for Borax, SB#534.

REPRODUCTION, MOUSE

DPR MEDICAL TOXICOLOGY

50366-081 098310 Fail, P.A., George, J.D., Grizzle, T.B., Heindel, J.J., and Chapin, R.E., "Final report on the reproductive toxicity of boric acid (CAS No. 10043-35-3) in CD-1 Swiss mice". Research Triangle Institute, 4/13/90. NTP Report #90-105. COBS Crl:CD-1* (ICR)BR VAF/PlusT outbred Swiss mice were placed in a continuous breeding program for 98 days. There were forty pairs of controls and 20 pairs each at doses of 1000, 4500, and 9000 ppm boric acid (98-99%) in diet. The last litters from the original F0 pairings provided F1 parents. The F1 parents were limited to control and 1000 ppm groups, due to total infertility (9000 ppm group) or very poor fertility (4500 ppm group). Selected F1 pups were maintained for 74 ± days on dose, then mated within dose groups for up to 7 days. These animals were necropsied at weaning of a single litter per pair. Meanwhile, a crossover study was performed, in which F0 adults, having completed the continuous breeding study, were mated as: control males X control females, 4500 ppm males X control females, or 4500 ppm females X control males. The analysis

of crossover study offspring was limited to fertility, litter size, and litter survival. Surviving F0 adults (except 1000 and 9000 ppm females) and F1 parents were necropsied and at least major reproductive organs were microscopically examined. NOEL = 1000 ppm (possible adverse effects: markedly reduced fertility, reduced litter sizes, increased % of pups born dead, smaller pup weights, apparent reduction in pup survival, germinal epithelium of males was markedly degenerated or atrophied, with hypospermia or aspermia, sperm were reduced in concentration and motility, and sperm abnormalities were increased). Adult effects included marked increase in water consumption at 4500 ppm and above. Not acceptable, not upgradeable: study did not evaluate viability of F2 offspring, only 1 dose was usable for 2-generation evaluation, and insufficient individual data were provided for some parameters. Aldous, 1/6/92.

50366-079 091186 and 091187 Exact duplicate of 081:098310.

TERATOLOGY, RAT

50366-082 098311 Price, C.J., Field, E.A., Marr, M.C., Myers, C.B., Morrissey, R.E., and Schwetz, B.A. "Final report on the developmental toxicity of boric acid (CAS No. 10043-35-3) in Sprague-Dawley rats". Research Triangle Institute, Research Triangle Park, NC., May 1, 1990. Crl:CD* BR VAF/PlusT Sprague-Dawley rats were dosed with boric acid in diet at 0, 0.1, 0.2, or 0.4% throughout the 20-day gestation period (29 dams/group). Groups of 14 dams were fed 0 or 0.8% boric acid in diets on days 6-15 in a parallel study. Maternal NOEL = 0.1 % (slight increases in kidney weight). The developmental NOEL = was not established (dose-related, statistically significant decreases in mean fetal weight were noted in all groups: also, "shortened rib XIII" and wavy ribs were dose-related at all dose levels). A "possible adverse effect" was indicated by a variety of effects, generally at higher doses, in the absence of marked maternal toxicity. These developmental effects included sharply increased resorptions (0.8% group), late fetal deaths (0.8% group), fetal weights reduced by about 1/3 to 1/2 (0.4% and 0.8% groups, respectively), gross malformations: short, curly tail (0.8% group), anophthalmia or microphthalmia (0.8% group); soft tissue malformations: enlarged lateral ventricles (0.4% and 0.8% groups), displaced eyes (0.8% group), various defects of

DPR MEDICAL TOXICOLOGY

heart and great vessels (0.8% group); skeletal malformations: agenesis of rib XIII (0.4% and 0.8% groups, related to "shortened rib XIII" noted above), fused ribs (0.8% group), cleft sternum (0.2%, 0.4% and 0.8% groups). A number of variations, many of which were ossification delays, were common in the 0.4% and 0.8% groups. Study is **not acceptable and not upgradeable** (no developmental NOEL). Aldous, 1/07/92.

50366-098 131754 Price, C.J., Marr, M.C., and Myers, C.B., "Determination of the No-Observable-Adverse-Effect Level (NOAEL) for developmental toxicity in Sprague-Dawley (CD*) rats exposed to Boric Acid (CAS No. 10043-35-3) in feed on gestational days 0 to 20 and evaluation of postnatal recovery through postnatal day 21", Research Triangle Institute, 8/8/94. RTI ID 65C-5657-200. Boric Acid, 98-99% purity, was administered in diet at 0%, 0.025%, 0.05, 0.075, 0.100 or 0.200% to 60 time-mated Sprague-Dawley female rats/group during gestation days 0 to 20. Scheduled sacrifice for about half of the dams per group was on gestation Day 20 (Phase I), and for the rest on post-natal Day 21 (Phase II, a recovery study). A "possible adverse effect" was seen: this study confirmed findings of the previous study (see Record No. 098311), and identified NOAELs for maternal and developmental changes. Maternal NOAEL = 0.100% in diet (reduced gravid uterine weight and slightly increased right kidney weight). Developmental NOAEL = 0.075%, based on increased incidence of shortened rib XIII, wavy ribs and reduced fetal body weight. For litters reared to weaning, a postnatal NOAEL = 0.100%, based on increased incidence of shortened rib XIII. This study is not independently acceptable, since is a follow-up study designed with specific objectives. Nevertheless, coupled with Record No. 098311, this report provides a coherent assessment of boric acid developmental toxicity. Kishiyama and Aldous, 12/16/94.

**"Peer Review" of 50366-082 098311, in conjunction with 50366-098 131754. Title and date of the primary study: "Final report on the developmental toxicity of boric acid (CAS No. 10043-35-3) in Sprague-Dawley rats", 5/1/90. The primary study, Record No. 098311, was classified as "not acceptable" due to lack of of a NOEL. An ancillary study, Record No. 131754, was then undertaken. The latter study identified a NOAEL for maternal and developmental effects, and also assessed postnatal recovery. Collectively, these studies fill

DPR MEDICAL TOXICOLOGY BORIC ACID AND RELATED INORGANIC BORATES T950120
Page 12

the rat teratology study "data gap". Overall, the studies continue to indicate a "possible adverse effect". Aldous, 12/16/94.

TERATOLOGY, RABBIT

** 50366-083 112056 Price, C.J., Marr, M.C., and Myers, C.B., "Final report on the developmental toxicity of boric acid (CAS No. 10043-35-3) in New Zealand White rabbits". Research Triangle Institute, Nov. 1991. Maternal NOEL = 125 mg/kg/day (modest reduction in body weight corresponding to modest reduction in food intake). 250 mg/kg/day does characteristically had vaginal bleeding over about a 10-day period after cessation of dosing. Three 250 mg/kg/day does aborted (vs. none in other groups): a possible treatment effect. Developmental NOEL = 62.5 mg/kg/day (agenesis of gall bladder at 125 and 250 mg/kg/day). Main findings at 250 mg/kg/day were resorptions (90% of implants), with cardiovascular malformations in remaining conceptuses (enlarged aorta, interventricular septal defects, pulmonary artery and aorta both arising from right ventricle). Report is acceptable, and identifies possible adverse effects at the high dose (with a sharp dose-response curve). Aldous, 7/24/92.

TERATOLOGY, MOUSE

**50366-082 098312 Field, E.A., Price, C.J., Marr, M.C., Myers, C.B., Morrissey, R.E., and Schwetz, B.A. "Final report on the developmental toxicity of boric acid (CAS No. 10043-35-3) in CD-1-Swiss mice". Research Triangle Institute, Research Triangle Park, NC, Aug. 11, 1989. Crl:CD-1* (ICR) VAF/PlusT outbred albino Swiss mice were dosed with boric acid in diet at 0, 0.1, 0.2, or 0.4% on days 0-17 p.c. No maternal NOEL was identified, due to dose-related increases in "renal tubule dilatation/regeneration". No developmental NOEL was found, since "pale spleen" was increased, dose-related, in all groups. For both maternal and developmental toxicity, 0.1% in diet appeared to be near to a no-effect level. The study is considered to indicate a "possible adverse effect", since there were increased resorptions at 0.4% and above, and fetal body weight decrements, and some skeletal malformations at 0.2% and above

(considering also the higher doses used in pilot study, which was briefly discussed in this record). These findings did not appear to be simply due to maternal toxicity. **Acceptable**. Aldous, 1/07/92.

GENE MUTATION

50366-051 35658, Griffin, T.S., 1978. The Toxicology of Boric Acid and Sodium Tetraborate: A Literature Review. (U.S. Borax Research Corp., Griffin, T.S., 8/29/78). Includes 2 references to articles related to mutagenic effects in bacteria. The first reported an increase in increase in back-mutation to streptomycin dependence (Demerec et al., 1951), but the second, considered by Griffin to be more sensitive, reported no significant mutagenic activity (Iyer and Szybalski, 1958). UNACCEPTABLE (summary information only). (Carlisle 8/11/87)

50366-070 065131 "Toxicology and Carcinogenesis Studies of Boric Acid in B6C3F₁ Mice (Feeding Studies)." (EG&G Mason Research Institute, October, 1987, NTP Report No. 324)
Boric acid, 99.7%; tested with <u>Salmonella typhimurium</u>, strains TA1535, TA1537, TA98 and TA100, at 0 (vehicle not stated), 33, 100, 333, 1000 or 1820 μg/plate, 20 minute incubation before adding agar and plating; with and without male Sprague-Dawley rat liver and Syrian hamster liver Aroclor 1254-induced S9 fraction; triplicate plates, two trials; data from one trial only as mean ± standard error; both trials stated to give similar results; single page report in Appendix C (page 88) of oncogenicity report; inadequate information - full report should be submitted; UNACCEPTABLE but no evidence of an adverse effect. Possibly upgradeable. (Gee, 6/21/89).

50366-070 065131 "Toxicology and Carcinogenesis Studies of Boric Acid in B6C3F Mice (Feed Studies)." (EG&G Mason Research Institute, October, 1987, NTP Report 324) Boric acid, 99.7% technical grade; tested with mouse lymphoma cells with and without S9 from Fischer 344 male rats, induced with Aroclor 1254; incubated for 4 hours with boric acid followed by a 48 hour expression time; concentrations of 0 (vehicle not stated), 1000, 1800, 2600, 3400, 4200 or 5000 μg/ml without S9 and 0, 1000, 2000, 3000, 4000 or 5000 μg/ml with S9; duplicate

cultures; two trials with data from one trial reported and statement that both trials gave similar results; two pages only in appendix C of oncogenicity study; TFT to select mutants; UNACCEPTABLE with inadequate reporting of study but possibly upgradeable with submission of a full report and results of both trials for evaluation; no evidence of an adverse effect. (Gee, 6/21/89).

- ** 50366-080 098306 "Salmonella/Microsome Plate Incorporation Assay of Boric Acid." (K. R. Stewart, SRI International, Study No. 2389-A200-91, 8/12/91) Salmonella strains TA1535, TA1537, TA1538, TA98 and TA100 were exposed to boric acid in the plate incorporation assay without S9 or with 4% or 10% Aroclor 1254-induced male rat liver activation. Concentrations were 0, 10, 50, 100, 500, 1000 or 2500 μ g/plate. Two assays with triplicate plates in each. No evidence of cytotoxicity at any concentration. Limit of solubility in water given as 50 mg/ml. No increase in revertants. Negative for an adverse effect. Acceptable. Gee, 12/9/91.
- ** 50366-080 098307 "Mouse Lymphoma Cell Mutagenesis Assay (tk+/- / tk-/-) of Boric Acid." (C. J. Rudd, SRI International, Study No. 2389-G300-91, 8/23/91) Boric acid, granular technical, >99% purity, was exposed to mouse lymphoma L5178Y cells for 4 hours with and without male rat liver S9 activation. Concentrations were 0 (medium), 1.2, 1.7, 2.45, 3.5 or 5 mg/ml. There were duplicate cultures and two independent trials. Positive controls were hycanthone methane sulfonate and 3-methylcholanthrene, both functional. There was no indication of a reproducible increase in mutation frequency. Acceptable. Gee, 12/10/91.

CHROMOSOMAL EFFECTS

50366-070 065131 "Toxicology and Carcinogenesis Studies of Boric Acid in B6C3F₁ Mice (Feed Studies)." (EG&G Mason Research Institute, October 1987, Report No. 324) Technical boric acid, 99.7%; tested with Chinese hamster ovary cells with and without S9 from Aroclor 1254 induced male Sprague-Dawley rat liver; incubated without S9 for 8-10 hours at 0 (DMSO), 500, 1000, 1500 or 2000 µg/ml followed by 2-3 hours with colcemid; with S9 at 1000, 1600, 2000 or

2500 μ g/ml, for 2 hours followed by an additional 8 - 10 hours incubation including 2-3 with colcemid; harvested by mitotic shake-off; scored 100 cells per concentration; positive controls of mitomycin C (-S9) and cyclophosphamide (+S9); no evidence of an adverse genotoxic effect; summary table only, page 91 of mouse oncogenicity study; UNACCEPTABLE with inadequate information - full study should be submitted for evaluation. (Gee, 6/21/89).

** 50366-080 098309 "Bone Marrow Erythrocyte Micronucleus Assay of Boric Acid in Swiss-Webster Mice." (K. G. O'Loughlin, SRI International, Study No. 2389-C400-91, 8/19/91)
Boric acid, granular technical, > 99% purity, was given on two consecutive days at 0 (water), 900, 1800 or 3500 mg/kg/day to 10/sex/group. Doses were based on 1) a range-finding study and 2) the stated maximum practical dose. 5/sex/group were sacrificed at 24 and at 48 hours.
Bone marrow from each animal was assessed for % PCE/RBC and % PCE with micronuclei. Urethane was given as a positive control to male mice and was functional. No evidence for induction of micronuclei formation in the bone marrow (or peripheral blood in the range-finding study).
Although there some differences from current suggested protocol, the study is acceptable with no adverse effect. Gee, 12/10/91.

DNA DAMAGE

DPR MEDICAL TOXICOLOGY

"Toxicology and Carcinogenesis Studies of Boric Acid in B6C3F Mice (Feed Studies)." (EG&G Mason Research Institute, October, 1987, Report No. 324 of NTP) Technical boric acid, 99.7%; tested with and without Aroclor 1254-induced male Sprague-Dawley rat liver S9; without S9 at 0 (medium and DMSO), 200, 300, 400 or 500 μ g/ml, 22-24 hours with BrdU added after 2 hours at 10 μ M and colcemid for 2-3 hours; with S9, at 0 (medium and DMSO), 250, 500, 1600 and 2000 μ g/ml, 2 hours followed by washing and an addition 26 hours including BrdU and colcemid; no justification of concentrations and no reporting of whether cytotoxicity was seen; no evidence of increase in sister-chromatid exchange; no indication of the number of cells scored; UNACCEPTABLE - inadequate reporting with a single summary table on page 91 of mouse oncogenicity report. Full study should be submitted for evaluation. (Gee, 6/21/89).

** 50366-080, 086 098308, 115317 "Evaluation of the Potential of Boric Acid to Induce Unscheduled DNA Synthesis in in vitro Hepatocyte DNA Repair Assay Using the Male F-344 Rat." (J. P. Bakke, SRI International, Study No. 2389-V500-91, 8/23/91, amendment 5/20/92) Boric acid, granular technical, >99% purity, was tested with primary hepatocytes from male F-344 rats, three cultures per concentration for 19 hours. Unscheduled DNA synthesis was measured by autoradiography. Concentrations in the first trial were 0 (medium), 10, 100, 250, 500, 1000 or 5000 μg/ml. In the second trial, concentrations were 0, 5, 10, 50, 100, 250, 500, 1000, 2500, 3800 or 5000 μg/ml. Thirty cells per slide for a total of 90 were scored per concentration. Data presented as summary only. Insufficient information for evaluation of a possible adverse effect. Initially evaluated as unacceptable, possibly upgradeable with submission of individual scores and toxicity information. Gee, 12/10/91. Submission of 115317 upgrades the study to acceptable status. Examination of the data for the 3 slides per concentration suggests a possible adverse effect with an increase in the nuclear grains but especially in the % in repair. Gee, 8/7/92.

50366-086 115317 Addendum to 098308. Contains the cytotoxicity information and the individual data for the slides scored. Gee, 8/7/92.

A rebuttal on the above study was submitted by the registrant objecting to the finding of a possible adverse effect in 098308. The document has been reviewed and considered. There is no change in status - the study remains acceptable with a possible adverse effect. Gee, 1/12/95.

NEUROTOXICITY

Not required at this time.

DPR MEDICAL TOXICOLOGY

- END OF SB-950-MANDATED STUDIES -

BORIC ACID AND RELATED INORGANIC BORATES T950120
Page 18

SUPPLEMENTARY STUDIES (INCLUDING SUBCHRONIC ANIMAL STUDIES)

DPR MEDICAL TOXICOLOGY

50366-047 959679 "90-Day Dietary Administration - Rats." (Hazleton Laboratories, VA, 12/12/62) Boric acid, 98.97 - 99.6%; fed in the diet to 10/sex/group at 0, 0.03, 0.1, 0.3, 1.0 or 3.0% of the diet (equivalent to 0, 0.00525, 0.0175, 0.0525, 0.175 and 0.525 nominal boron equivalent); all animals at 3% died before the end of the study; testicular atrophy in all males at 1.0% and 1/10 at 0.3%; ovaries and uterus showed no effect; body weights at 1.0% were -48% of controls for males -15% for females; supplementary data. No worksheet. (Gee, 7/7/89.)

50366-047 959680 "90-Day Dietary Feeding - Dogs." (Hazleton Laboratories, VA, 1/17/63) Boric acid, no purity stated; fed in the diet at 0, 100, 1000 or 10,000 ppm (equivalent to 17.5, 175 and 1750 ppm as elemental boron) to 5/sex/group; at 10,000 ppm (1.0%), all males showed severe atrophy of the testes with degeneration of the spermatogenic epithelium; changes in the adrenal glands at 1.0% in 3/5 females; testes weights lower in 1000 and 10,000 ppm group males; uterus not examined in females; supplementary data. No worksheet. (Gee, 7/7/89).

DPR MEDICAL TOXICOLOGY

50681-005 067518 Weir, R.J., "90-day dietary administration - rats with 20 MULE TEAM*
Borax (Sodium tetraborate decahydrate)". Hazleton Laboratories, Inc., Falls Church, VA, Feb.
15, 1963. Male Charles River Sprague-Dawley pathogen-free rats were dosed with 0, 154, 463,
1540, or 4630 ppm borax (10/group). After 13 weeks, testes were histologically examined in
all rats. There were no changes in body weights, clinical observations, or gross appearance
of various organs, nor were there histological changes in the testes. Study is unacceptable
(not designed to fill a data requirement), but provides useful data. No adverse effect is
indicated. Aldous, 1/15/92. Note: this study was undertaken due to the unanticipated low
LEL for testicular atrophy in an earlier study (record No. 067517, see below).

50681-005 067517 "90-Day Dietary Administration - Rats 20 Mule Team* Borax (Sodium tetraborate decahydrate)", (O. E. Paynter, Hazleton Laboratories Inc., December 13, 1962). Borax, purity assumed to be 100%, was administered in the feed at nominal concentrations of 0, 463, 1540, 4630, 15400, or 46300 ppm to 10 Sprague-Dawley rats/sex/group for 90 days. A "possible adverse effect" is indicated: testicular atrophy was observed in 10, 1, 0, and 4 males in the 15,400, 4,630, 1540, and 463 ppm groups, respectively. No NOEL was identified, due to the puzzling results, above. All 46,300 ppm rats died, as did one male at 15,400 ppm. The low dose testicular effect appears suspect, based on inconsistent effects in this study and lack of corresponding low dose effects in other subchronic and longer term rat studies. Study is not acceptable, due to numerous deviations from modern guidelines but subchronic studies are not required under SB-950. Kishiyama and Aldous, 1/15/92.

HUMAN EPIDEMIOLOGICAL DATA

50366-088 118238 Whorton, D., Haas, J., and Trent, L., "Reproductive effects of inorganic borates on male employees: Birth rate assessment", ENSR Health Sciences, 3/31/92. A retrospective study showed that wives of workers from a borate mining and processing plant in Boron, CA delivered somewhat more children than expected numbers, based on a national cohort. This result led investigators to conclude that borate exposure to workers had no deleterious effect on their reproductive health. Study provides useful epidemiological information,

especially because testicular atrophy and subsequent male infertility had been observed in animal studies. Because of the limited scope of this study (live births as the sole endpoint), and limitations in design (birth rates compared to national norms, possibly inappropriate for a control population; exposures were only roughly estimated), this study

does not substitute for a reproduction study in laboratory animals. Aldous, 12/21/94.

DPR MEDICAL TOXICOLOGY

50366-088 118456 Whorton, D., Haas, J., and Trent, L., "Reproductive effects of inorganic borates on female employees: Birth rate assessment", ENSR Health Sciences, 3/31/92. This was an offshoot to the study performed to evaluate reproductive effects on male employees (see Record No. 118238), and was presented as Appendix C of that report. The study on female employees also monitored the same endpoints: numbers of live births and sex of offspring compared to the same national database. There were only 68 female participants in this study, thus very limited opportunity to identify treatment effects. Results were not remarkable. The study should be considered as useful epidemiological data, but more limited in statistical power than the corresponding data on male employees. Other limitations noted for the male employee study also apply here. Aldous, 12/21/94.

50366-088 118457 Wegman, D.H., Eisen, E.A., and Smith R.G., "Acute and chronic respiratory effects of sodium borate particulate exposures", 1/3/91. Only chronic aspects of this study are summarized here. Pulmonary function studies were conducted in 1981 and 1988 at the U.S. Borax mine near Boron, CA. There were 303 participants with usable tests [forced vital capacity (FVC), and forced expiratory volume in 1 second (FEV $_1$)] during both time periods. Chief criteria examined were decrements in the above measures over the 7-year period between tests. Estimates were made of dust and borate exposures, based on job classifications. Analyses considered variables such as age and smoking histories. Results indicated no association between exposure and pulmonary function during the 7-year period. Useful information, but not a substitute for animal chronic studies for many reasons, including that exposure was not rigorously characterized, only a single set of endpoints was evaluated (pulmonary function changes), the exposure timeframe did not include the whole period of workers' exposure (so that initial pulmonary changes, if any, might be detected). Aldous, 12/21/94.